

REMARKS

I. Status of the claims

After entering this amendment, claims 1-8, 11-23, 28, 29, and 39-46 will be pending in this application. Claims 3 and 41-44 have been withdrawn by the Office for being directed to non-elected subject matter. Claim 9 and claim 10 have been canceled and their subject matter is now claimed in new independent claims 45 and 46. Support for claims 45 and 46 can be found, for example, in the original claims. Thus, no new matter has been introduced by the amendments to the claims.

II. Rejections under 35 U.S.C. § 112

Claims 1, 22, 23, 28, and 29

Claims 1, 22, 23, 28, and 29 stand rejected under 35 U.S.C. 112, first paragraph for allegedly failing to comply with the written description requirement. Office Action at 2. More specifically, the Office alleges that the claim limitation “wherein the solvent evaporates after application of the said composition to a skin surface” is not supported by the passage on page 9 of the specification, as previously indicated by Applicants. *Id.* Applicants respectfully traverse this rejection.

Applicants point out that explicit support for the limitation at issue is contained within the second complete paragraph of page 9 of the as-filed specification (lines 19-24). That text states that:

Film-forming agents are substances of varying composition which have the feature that, when dissolved in water or other suitable solvents, *they form films on the skin after the water or the solvent has evaporated*, these films being capable, *inter alia*, of releasing incorporated active compounds in a controlled manner over a certain period of time.

Specification at 9, ll. 19-24 (emphasis added). The limitation “wherein the solvent evaporates after application of the said composition to a skin surface” finds textual support in the phrase “[film-forming agents, when dissolved in water or other suitable solvent] form films on the skin after the water or the solvent has evaporated.” This passage clearly conveys to one of ordinary skill in the art the recitation “wherein the solvent evaporates after application of the said composition [comprising the solvent] to a skin surface.” Nothing more is necessary to satisfy the written description requirement. Applicants respectfully remind the Office that the specification need not recite the language in the claim *ipsis verbis*. M.P.E.P. § 2163.II.A.3(a). Rather, the test is “whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed.” M.P.E.P. § 2163.02. That is, the question is whether Applicants were in possession of compositions in which “the solvent evaporates after application of the said composition to a skin surface” at the time of filing. The cited passage on page 9 of the specification clearly answers that question in the affirmative. Accordingly, Applicants respectfully request that the rejection under U.S.C. § 112 be withdrawn, at least for the foregoing reasons.

III. Rejections under 35 USC § 103

Claims 1, 2, 4-8, 11-14, 22, 23, 28, 29, and 40 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 5,411,981 (“*Gaillard*”), in view of U.S. Patent No. 4,946,870 (“*Partain*”), US Patent No. 5,658,559 (“*Smith*”), US Patent No. 5,753,251 (“*Mougin*”), and Cremophor® RH 40 Technical Information, 1997 (“the *Cremophor® pamphlet*”). Office Action at 3.

Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over *Gaillard, Partain, Smith, Mougin* and the *Cremophor® pamphlet* as applied to claims 1, 2, 4-8, 11-14, 22, 23, 28, 29, and 40 as above, and further in view of *Ismail* (US 5541220).

Id. at 7.

Claims 18 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Gaillard, Partain, Smith, Mougin* and the *Cremophor® pamphlet* as applied to claims 1, 2, 4-8, 11-14, 22, 23, 28, 29, and 40 as above, and further in view of *Gaetani et al.* (EP 0427625 A). *Id.*

Claims 18 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Gaillard, Partain, Smith, Mougin* and the *Cremophor® pamphlet* as applied to claims 1, 2, 4-8, 11-14, 22, 23, 28, 29, and 40 as above, and further in view of Applicants' own disclosure and *Hocquaux et al.* (WO 92/21317). *Id.* at 8.

Claims 18 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Gaillard, Partain, Smith, Mougin* and the *Cremophor® pamphlet* as applied to claims 1, 2, 4-8, 11-14, 22, 23, 28, 29, and 40 as above, and further in view of *Hocquaux et al.* (WO 91/19701). *Id.* at 9.

Applicants respectfully traverse these rejections. A *prima facie* case of obviousness, the requirements of which are discussed below, has not been established for each rejected claim.

A. The Office's rejection—*Gaillard* in view of *Partain, Smith, the Cremophor® pamphlet, and Mougin*

According to the Office, *Gaillard* teaches that formula (I) compounds of the instant claims have anti-androgenic activity and are used in pharmaceutical compositions including creams, pomades, and lotions. Office Action at 3. (citations

omitted). In particular, the Office asserts that the formula (I) compound, 4-[3-(4-hydroxybutyl)-2,5-dioxo-1-imidazolidinyl]-2-(trifluoromethyl)benzonitrile, which is recited in instant claim 4 is also disclosed in Example 96 of *Gaillard*. *Id.* The Office also alleges that *Gaillard* teaches “that the compositions are ‘useful in dermatology’ and can be used with other anti-acne components such as retinol or with a product stimulating the growth of hair such as Minoxidil (6-amino-4-4-piperidino-1, 2-dihydro-1-hydroxy-2-iminopyrimidine) for the treatment of alopecia;” further asserting that *Gaillard* teaches adding a 5-alpha-reductase inhibitor to the composition, which in the Office's view “meets instant claims 16 and 17.” *Id.*

With regard to *Partain*, the Office asserts that it “teaches a topical film-forming composition for delivering pharmaceutical actives with controlled release;” further stating that “[t]he reference teaches that the composition is useful as a delivery system for single or [a] combination of pharmaceutical active agents, including anti-acne agents (retinoic acid and benzoyl peroxide) and anti-aloepecia agents (Minoxidil).” *Id.* at 3-4. (citations omitted). According to the Office, *Partain* discloses the delivery of several pharmaceutically active agents and asserts that *Partain* teaches that “chitosan derivatives are useful film formers and topically applied in the form of lotion, solution, cream, etc.” *Id.* at 4. Further according to the Office, *Partain* “provides the general teaching of using a film-forming agent as a controlled-release delivery system for anti-acne and anti-aloepecia agents, either alone or in combination with other pharmaceutical agents,” and teaches of use of solvents “such as ethanol or glycerin with the chitosan film forming agent. *Id.*

The Office relies on *Smith* is because it allegedly "also teaches a film-forming lotion composition which forms [a] barrier on the surface of the skin to prevent evaporative loss of moisture from the skin, and protects the skin from environmental irritants." *Id.* at 4-5. According to the Office, *Smith* teaches "polyquaternary polyvinylpyrrolidone such as polyquaternium-16 (polyvinylpyrrolidone/imidazolinium methochloride copolymers)," which is recited by instant claim 40. *Id* at 5. The Office also apparently attempts to relate *Smith*'s disclosure that "[i]sopropanol is used as a solvent to dissolve pharmaceutical actives" to the fact that isopropanol is recited by instant claim 8. *Id.* The Office also points out that the pharmaceutical actives taught by *Smith* include the anti-acne actives, benzoyl peroxide and vitamin A. *Id.*

After correctly noting that the foregoing cited references fail to disclose Applicants' elected plasticizer, polyoxyethylated hydrogenated castor oil, or any other plasticizer for that matter, the Office relies on *Mougin* for its disclosure of polyoxyethylated hydrogenated castor oil, in the form of Cremophor® RH 40. Specifically, the Office states that:

Mougin teaches film-forming compositions for topical use. The reference teaches adding a plasticizing agent to the solution of the organic solvent in a proportion between 5-40% by weight relative to the weight of the film-forming polymer, for the purpose of improving the cosmetic and mechanical properties. See col. 5, lines 46 - col. 6, line 22. POE hydrogenated castor oil is among the possible hydrophilic plasticizing agents. See also Example 15.

Id. at 5. (citations omitted). The Office also asserts that *Mougin* "indicates that isopropanol, which is used in *Smith*, is a volatile solvent." *Id.* (citations omitted).

Finally, the Office states that the *Cremophor*® pamphlet "teaches that POE hydrogenated castor oil is skin compatible and solubilizes hydrophobic pharmaceuticals

including vitamin A (retinoic acid);” and that “[t]he reference teaches that the product forms clear solutions in water and ethanol with fatty acids and fatty alcohols.” *Id.* (citation omitted).

The Office summarizes its rationale for why the cited references allegedly render the rejected claims obvious by stating that:

Partain and Smith would have obviously motivated one of ordinary skill in the art at the time the present invention to modify the teaching of Gaillard and formulate the active ingredients in a controlled-release composition because (a) Partain teaches that a film-forming composition “acts as a reservoir to continuously and uniformly deliver the actives as well as protect the tissue from further injury or insult, which negates the need for hair cover, and controls the dosage at a constant level; (b) Smith also teaches a film-forming formulation which provides controlled-release of the actives while protecting the skin and prevent loss of moisture of the skin.

Id. at 5-6. The Office further alleges that a skilled artisan would have had a reasonable expectation of success “producing a stable and effective film-forming lotion which is useful for treating acne or alopecia, and delivering the active agents in a controlled, constant dosage, while protecting the application site. *Id.* In order to show alleged teachings of the plasticizer aspect of the instant invention by the cited art, the Office turns to *Mougin*, asserting that:

“[i]t would have been obvious to one of ordinary skill at the time the invention was made to modify the composition of the combined references by adding POE hydrogenated castor oil as motivated by Mougin and Cremophor because (a) Smith, Gaillard, and Cremophor all teach using retinoic acid; and (b) Cremophor teaches that POE hydrogenated castor oil is a well-known solubilizer in pharmaceutical/cosmetic art, which solubilizes hydrophobic pharmaceutical agents to form a clear solution.”

Id. The Office alleges that a skilled artisan would have had a reasonable expectation of success of “producing a stable, clear film-forming composition comprising the

compound of instant formula (I) which provide [sic] improved cosmetic and mechanical properties.” *Id.* Applicants respectfully disagree with the Office’s reasoning and traverse this rejection for the following reasons.

B. The Office improperly relies on hindsight to allege that the addition of a plasticizer would have been taught by the combined cited art

The Office’s explanation or reasoning as to why one of ordinary skill in the art would have combined the disclosures of *Mougin* and the *Cremophor® pamphlet* with the remaining cited art improperly relies on hindsight gleaned from Applicants own disclosure. M.P.E.P. §2141.II. The Office argues that “it would have been obvious to one of ordinary skill . . . to modify the composition of the combined references by adding POE hydrogenated castor oil as motivated by *Mougin* and *Cremophor* because (a) *Smith*, *Gaillard*, and *Cremophor* all teach using retinoic acid; and (b) *Cremophor* teaches that POE hydrogenated castor oil is a well-known solubilizer in pharmaceutical/cosmetic art, which solubilizes hydrophobic pharmaceutical agents to form a clear solution.” Office Action at 6.

However, the Office has nonetheless failed to explain why the artisan would have looked to *Mougin* when *Mougin* does not disclose film-forming compounds, plasticizers, active agents, or uses of compositions that overlap with any of the other cited references. While the Office states that “*Mougin* teaches adding a plasticizer improves the cosmetic and mechanical properties of a film-forming topical composition” (Office Action at 6), Applicants point out that *Mougin* fails to define what those properties are, and fails to provide information that would have allowed one of ordinary skill in the art to determine the desirability of those properties in the context of the disclosures of *Smith* and *Partain*. Thus, one of ordinary skill in the art would not have known how such a

teaching could have been applied to the teachings of *Smith* and *Partain* to arrive at the instantly claimed invention. Hence, Applicants respectfully submit that one of ordinary skill in the art would have had to rely on hindsight to include *Mougin*'s teachings pertaining to plasticizers.

The M.P.E.P. clearly warns that "[a] statement that modifications of the prior art to meet the claimed invention would have been 'well within the ordinary skill of the art at the time the claimed invention was made' because *the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a prima facie case of obviousness without some objective reason to combine the teachings of the references.*" M.P.E.P. § 2143.01.IV (underling in original; italics added, internal citations omitted.) The M.P.E.P. further explains that "rejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *Id.* (citing from *KSR International Co. v. Teleflex Inc.*, 82 U.S.P.Q.2d 1385, 1396 (2007)).

Applicants remind the Office that "the focus when making a determination of obviousness should be on what a person of ordinary skill in the pertinent art would have known at the time of the invention, and *on what such a person would have reasonably expected to have been able to do in view of that knowledge.*" M.P.E.P. §2141.II (emphasis added, citing from *KSR*).

The Office particularly refers to Example 15 of *Mougin* as being indicative of teachings related to the use of polyoxyethylated hydrogenated castor oil as a plasticizing agent. However, Applicants respectfully point out that Example 15, which

describes a lotion for hair styling, does not disclose polyoxyethylated hydrogenated castor oil, or a plasticizer. Instead, Applicants believe the Office intended to refer to Example 16, which describes a mouthwash composition that includes polyoxyethylated hydrogenated castor oil as an ingredient. None of the other 29 examples teach the inclusion of polyoxyethylated hydrogenated castor oil. Assuming that the Office meant to rely on Example 16 to exemplify the use of polyoxyethylated hydrogenated castor oil as a plasticizer, Applicants submit that one of ordinary skill in the art would have had no reason to look to a mouthwash composition for teachings related to *film-forming compositions capable of releasing compounds of formula(I) to the skin surface*. This highlights the Office’s use of improper hindsight in its obviousness analysis.

The teachings of *Mougin* would not have led one of ordinary skill in the art to use a plasticizer in the compositions of *Smith* or *Partain* because *Mougin* fails to teach compositions that contain any active agents that are delivered from a film to the skin surface. All *Mougin* compounds contain pseudo-latex polymers, which are the sole film-forming polymers taught therein, but there are no teachings in *Mougin*, or the other cited references, suggesting that pseudo latex polymers are compatible with the release of active agents to the skin surface. Therefore, even if *Mougin* discloses plasticizers that improve “the cosmetic and mechanic properties” of a composition, one of ordinary skill in the art reading *Mougin* in context would not have been led to add a plasticizer to the compositions of *Partain* or *Smith* because *Mougin*’s compositions are directed to a use different from those of *Partain* or *Smith*. For example, *Mougin* explains that “the subject of the present invention is cosmetic compositions in the form of *shampoo, conditioner, a styling or treating lotion or gel or a hair shaping product, or alternatively in*

the form of a make-up product such as a mascara or a nail varnish.” *Mougin* at col. 1, II. 9-12 (Emphasis Added.). Therefore, a skilled artisan would not have looked to *Mougin* for teachings of a plasticizer to include in a composition intended for delivery of active ingredients to skin.

Moreover, Applicants point out that new independent claims 45 and 46, which are directed to the subject matter of canceled claims 9 and 10, recite film-forming agents that are chosen only from specified groups of agents that do not include film-forming agents comprising the pseudo-latex polymers disclosed in *Mougin*. Thus, at a minimum, Applicants submit that a skilled artisan would not have looked to *Mougin* for teachings of any alleged advantage of adding plasticizers to film-forming compositions to arrive at the subject matter of claims 45 and 46 because the film-forming agents in *Mougin* are different from those in claims 45 and 46 and the cited references fail to suggest that the alleged advantages of using a plasticizer with pseudo-latex polymers would have been expected in systems that use other film-forming agents.

Indeed, to establish a *prima facie* case of obviousness, the Examiner must make a determination whether the claimed invention “as a whole” would have been obvious at that time to that person. Knowledge of applicant’s disclosure must be put aside in reaching this determination, yet kept in mind in order to determine the “differences,” conduct the search and evaluate the “subject matter as a whole” of the invention. M.P.E.P. § 2142. The Office cannot pick and choose from a reference only what is needed to support a given position to exclusion of other parts necessary to appreciate what reference suggests. *In re Inland Steel*, 265 F.3d 1354, 60 U.S.P.Q.2d 1396 (Fed.

Cir. 2001). The Office must consider the claimed invention as a whole. *Loctite Corp. v. Ultraseal Ltd.*, 781 F.2d 861, 228 U.S.P.Q. 90 (Fed. Cir. 1985).

"There must be a reason or suggestion in the art for selecting the procedure used, other than the knowledge learned from the applicant's disclosure" *In re Dow Chem. Co. v. American Cyanamid Co.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531-32 (Fed. Cir. 1988). Thus, the burden is on the Office to provide a tenable rationale as to, (1) *why* one of ordinary skill in the art would have looked from the teachings of *Gaillard*, *Partain*, *Smith*, and the *Cremophor® pamphlet*, to *Mougin* for teachings or suggestions to include a plasticizer in a film-forming composition for the delivery of a compound of formula (I) to a skin surface; and (2) *why* one of ordinary skill at the time the invention would have made the combinations and/or modifications necessary to arrive at the claimed invention without relying on hindsight. See M.P.E.P. § 2141(III) ("[The Office] must explain why the difference(s) between the prior art and the claimed invention would have been obvious to one of ordinary skill in the art"), §2142. As explained above, the Office has failed to do so in this case.

C. One of skill in the art would not have had an expectation of success in achieving the claimed invention by combining the teachings of the cited art

One of ordinary skill in the art could not have looked to *Mougin* to find teachings of a plasticizer, without overlooking the fact that *Mougin* does not provide teachings of plasticizers beyond their limited use in compositions containing pseudo-latex compounds. Furthermore, pseudo-latex compounds are neither disclosed by the other cited references, nor does *Mougin* address the issue of whether or not pseudo-latexes have the capacity to release active agents from films formed on skin surfaces. The Office also relies on *Mougin* to assert that "Mougin teaches that adding a plasticizer

improves the cosmetic and mechanical properties of a film-forming topical compositions,[sic]” Office Action at 6. However, as mentioned before, *Mougin* fails to provide information about the “cosmetic and mechanical, properties” so that one of ordinary skill in the art could determine whether such cosmetic and mechanical, properties are desired in other systems that use film-forming agents different from those used in *Mougin*. Thus, a skilled artisan would not have known if the properties imparted to the film-forming composition of *Mougin* by the plasticizer of *Mougin* were desirable in the systems disclosed in, for example, *Smith* and *Partain*. In essence, even if the teachings of the cited art were to be combined, none of the cited references explain how the pseudo-latex polymer-based compositions of *Mougin* would affect the function of the other ingredients of the claimed composition, including compounds of formula (I). Thus, one of ordinary skill in the art would not have had a reason to expect that addition of the plasticizers disclosed in *Mougin* would have been compatible with the delivery systems taught in *Partain* or *Smith*.

In order to create a *prima facie* case of obviousness, the U.S. Supreme Court in *KSR Int'l Co. v. TeleFlex Inc.* emphasized the need to explain how the combination of references would have given one of ordinary skill in the art a reasonable expectation of success. M.P.E.P. § 2143.02 (citing *KSR*, 127 S.Ct. 1727, 1733 (2007)). Here, the Office has not met its burden because it has failed to explain how one of ordinary skill in the art would have been expected to combine the teachings of *Mougin*, which do not relate to the release of an active agent from a film formed on a skin surface, with the other cited references to obtain a composition that would have been capable of successfully releasing a compound of formula (I) from the film, as instantly claimed.

Assuming that the teachings of the cited references even could be combined in such a way to render the instant invention obvious, “[t]he mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art” at the time the invention was made. M.P.E.P. §2143.01(III) (internal citation omitted). It is improper to “[use] that which the inventor taught against its teacher.” *In re Lee*, 277 F.3d at 1343 (citing *W.L. Gore v. Garlock, Inc.*, 721 F.2d 1540, 1553, 220 U.S.P.Q. 303, 312-13 (Fed. Cir. 1983)). Furthermore, even if it were possible for one of ordinary skill in the art to pick and choose from among the teachings of the cited art in order to arrive at the claimed formulation, the artisan would not have had a reason to expect that the combination of references would have produced a successful formulation as claimed, unless the artisan relied on the teachings of the instant invention. In fact, the cited art contains warnings of the pitfalls one may face when compatibilities among compound components are not properly considered. For example, *Smith* teaches that “[t]he therapeutic agents should be chemically compatible with the other ingredients of the composition.” *Smith* at col. 4, ll. 47-48. The *Cremophor® pamphlet* advises that “Cremophor RH40 may alter the rate of absorption of active substances.” The *Cremophor® pamphlet* at 6. In addition, the instant specification explains that “precipitates of the substances at the application site after evaporation of the solvent” occurred with conventional aqueous/alcoholic hair lotions. Specification at p. 3, line 25 to p. 4, line 5. Thus, Applicants respectfully submit that the Office has not met its burden of showing that one of ordinary skill in the art would have expected that the combination of references would have functioned as claimed, as required by *KSR* and

the M.P.E.P. to establish a *prima facie* case of obviousness. Accordingly, Applicants respectfully submit and request that the rejection of the claims under 35 U.S.C. § 103(a) be withdrawn.

D. The Office's reasons to combine the references do not apply to claim 23

Claim 23 is an independent claim that is directed to a process for the treatment of androgenic alopecia, which is a condition that none of cited references teach as being treatable by retinoic acid or retinoid-based therapies. By contrast, the Office's arguments for combining *Gaillard* with *Pertain*, *Smith*, and the *Cremophor® pamphlet* have been focused on the Office's allegation that *Gaillard* teaches that the instant compounds of formula (I) can be combined with retinoids for the treatment of acne. Office Action at 5-6. According to the Office, the film-forming compositions of *Pertain* can also be used to deliver retinoic acid (*Id.* at 3), and the *Cremophor® pamphlet* teaches that *Cremophor® RH 40* is a solubilizer for retinoic acid (*Id.* at 5).

However, even assuming, *arguendo*, that one of ordinary skill in the art would have combined the references for the purpose suggested by the Office, such combination does not apply to claim 23. Retinoic acid and retinoids in general are useful in the treatment of acne because of their antibiotic properties. *Gaillard* at col. 9, II. 56-59. Given that claim 23 is directed to the treatment of androgenic alopecia, and that none of the references teaches or suggests the use of antibiotics (or retinoids) for the treatment of alopecia, one of ordinary skill in the art would not have had a reason to combine the references as suggested by the Office. Applicants also submit that, based on the Office's own arguments, the skilled artisan would have not looked to *Mougin* for teachings of plasticizers in view of the other cited references, because the other cited

references could not have been combined without using teachings of retinoids to thread them together. Accordingly, for the additional purpose of the treatment of androgenic alopecia, a disorder that the cited art does not teach as being treatable with retinoid-based therapeutic agents, claim 23 is not obvious and Applicants respectfully request that this rejection be withdrawn.

IV. Conclusion

In view of the foregoing remarks, Applicants submit that this claimed invention is neither anticipated nor rendered obvious in view of the prior art references cited against this application. Applicants therefore request the Office's reconsideration of the application, and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account 06-0916.

Respectfully submitted,

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